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LETTER TO THE EDITOR

Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?

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Abstract

Use of newer antipsychotics for substitution of current antipsychotics might be one way awaiting to be clinically verified to address antipsychotic cardiotoxic effects. Alternatively, the combination of existing antipsychotics with cardioprotective agents is also beneficial for patients with mental disorders for avoiding cardiotoxicity to the maximum.

Key Words: Antipsychotics; Cardiotoxicity; Combined medication; Adjunct therapy

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Core Tip: The newer antipsychotics have been reported to have fewer side effects and better performance in efficacy in short-term studies. Still, a dilemma lies between the benefit of ameliorating psychotic symptoms and severe side effects especially life-threatening cardiotoxicity in antipsychotic medications in clinical practice. The combination of antipsychotics with other therapeutic agents providing cardioprotection, such as β-blockers, cannabinoid 1 receptor antagonists, cannabinoid 2 receptor agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and ω-3 polyunsaturated fatty acids, may represent a promising strategy and sweet pledge.

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TO THE EDITOR

We read with interest a recent paper entitled "Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise" by Barman *et al*[1] published in this journal[1]. The paper appraised the scientific data on psychopharmacology, safety profile, and efficacy of the newer antipsychotics, namely, brexpiprazole, cariprazine, and lumateperone. The authors compared the characteristics and indications of the three newer antipsychotic agents to indicate their promising future in treating schizophrenia in the short term, particularly due to their properties of less metabolic toxicity and potential control of negative symptoms.

In previous studies, several toxic effects were revealed in the use of first-generation antipsychotics and second-generation antipsychotics (SGAs), especially the life-threatening cardiotoxicity. The manifestations of cardiotoxicity range from heart rate change (*e.g.*, bradycardia or tachycardia) and blood pressure alternation (*e.g.*, hypotension or hypertension) to fatal issues such as QT prolongation and congestive heart failure. The three newer antipsychotics mentioned in the article are typical third-generation antipsychotics (TGAs), which display well-documented lower metabolic liability and better performance in targeting negative symptomatology and improving cognitive domains[2]. In addition, some TGAs such as roliperidone are associated with a lower incidence of cardiovascular side effects in short term. However, long-term clinical studies are limited, leading to a deficiency in clinical evidence of TGA cardiotoxicity. Further clinical trials are needed to determine whether TGAs perform better than their precursors in both safety and efficacy.

Given that the clinical application of TGAs is still under debate, the combination of existing antipsychotics with other therapeutic agents in the treatment of mental disorders, especially the cardioprotective agents, may also represent a promising strategy. Several therapeutic agents which are promising in combined medications are listed in Table 1. β-adrenal receptor blockers, as classical antiarrhythmic agents, have been verified to offer symptomatic relief in patients who suffer from tachycardia [3]. Some researchers have reached a consensus that optimal doses of β-blockers like propranolol can be well tolerated and are effective in alleviating clozapine-induced tachycardia and myocarditis[4]. In our serial works, we elaborated that both cannabinoid 1 receptor (CB1R) and cannabinoid 2 receptor (CB2R) were critically involved in SGAs-induced cardiac side effects and played opposite roles in the process of toxicity[5,6]. Administration of SGAs (clozapine or quetiapine) in 2-3 wk caused a decrease in CB1R but an increase in CB2R expression in a dose- and time-dependent manner. The functional rivalry between CB1R and CB2R suggests that specific antagonists of CB1R or agonists of CB2R could relieve antipsychotic cardiotoxicity, such as inflammation suppression and myocardial fibrosis remission. Of note, the opposite effects of cannabinoid receptors suggest that adjunct therapy should be based on single cannabinoid receptor agonism or antagonism since dual agonism/antagonism would unfortunately yield neutralizing effects[7]. In addition, CB1R antagonists have been marketed for weight loss, and CB2R agonists have also been shown to maintain metabolic process[8]. The use of CB1R antagonists or CB2R agonists in combination with antipsychotics might thus exert dual clinical benefits: One to inhibit drug cardiac toxicity and the other to attenuate antipsychotic-induced glycolipid metabolic disorders. Since cardiovascular and metabolic adverse effects compose the major concerns associated with SGAs use, the potential dual benefits derived from CB1R antagonists or CB2R agonists seem to be particularly important in the clinic[9]. However, since individual antagonists of CB1R like rimonabant may cause additional psychiatric disorders due to brain penetrance, development of beneficial CB1R antagonists or CB2R agonists that are peripherally restricted could assuage the clinical concerns.

In addition to those G protein-coupled receptor-based adjunct strategies, our recent animal study also suggested that pharmacological inhibition of intracellular spliceosome signaling at a relatively low concentration might also confer cardioprotection against SGAs cardiotoxicity[10]. Since clozapine cardiotoxicity is mainly manifested as cardiac inflammation (myocarditis), inhibition of oxidative stress and proinflammatory cytokines (*e.g.*, tumor necrosis factor-α) were also shown to be protective against clozapine-induced cardiotoxicity[11-13]. Current studies further showed that omega-3 polyunsaturated fatty acids (ω-3 PUFAs) were beneficial for schizophrenia patients in view of its protections against cardiovascular morbidity and mortality[14]. Of note, the dose-related cardioprotective and antiarrhythmic effects of ω-3 PUFAs have been observed in large clinical trials and consequently, this outcome may have provided strong evidence for ω-3 PUFAs becoming a potential candidate in the combined medication[15].

In summary, we are in agreement with the conclusion in the main body of the paper that all three newer antipsychotic agents are promising in the treatment of psychiatric disorders based on short-term studies. However, long-term studies are still limited to provide further evidence for systematic comparison between newer antipsychotics and their precursors. Thus, we put forward that the combination of existing antipsychotics with other cardioprotective agents, such as β-blockers, CB1R antagonists, CB2R agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and ω-3 PUFAs, may reach the expectation that the combined medication can avoid the severe adverse effects of antipsychotics to the maximum in the treatment of mental disorders. The peripherally-restricted CB1R antagonists or CB2R agonists might merit further large clinical trials since they might provide beneficial control of SGAs-induced both metabolic and cardiac side effects.

Table 1 Therapeutic agents for potential adjunct therapy in combination with existing antipsychotics

Therapeutic agents	Beneficial effect	Ref.
β-adrenal receptor blockers	Alleviating tachycardia and myocarditis	[3,4]
CB1R antagonists	Suppressing inflammation, ameliorating myocardial fibrosis	[5,6]
CB2R agonists	Suppressing inflammation, ameliorating myocardial fibrosis	[5,6]
Spliceosome inhibitors (*e.g.*, pladienolide B)	Inhibition of SGAs-induced alternative splicing events and consequent amelioration of inflammation and myocardial cell death	[10]
ACEIs (*e.g.*, captopril)	Oxidative stress and proinflammatory cytokine inhibitors	[11-13]
ω-3 PUFAs	Anti-arrhythmia	[15]

ACEI: Angiotensin-converting enzyme inhibitor; PUFAs: Polyunsaturated fatty acids; SGA: Second-generation antipsychotics; CB1R: Cannabinoid 1 receptor; CB2R: Cannabinoid 2 receptor.

FOOTNOTES

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